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Effort-Related Motivational Effects of the VMAT-2 Inhibitor Tetrabenazine: Implications for Animal Models of the Motivational Symptoms of Depression

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Motivated behaviors are often characterized by a high degree of behavioral activation, and work output and organisms frequently make effort-related decisions based upon cost/benefit analyses. Moreover, people with major depression and other disorders often show effort-related motivational symptoms such as anergia, psychomotor retardation, and fatigue. It has been suggested that tasks measuring effort-related choice behavior could be used as animal models of the motivational symptoms of depression, and the present studies characterized the effort-related effects of the vesicular monoamine transport (VMAT) inhibitor tetrabenazine. Tetrabenazine produces depressive symptoms in humans and, because of its selective inhibition of VMAT-2, it preferentially depletes dopamine (DA). Rats were assessed using a concurrent fixed-ratio 5/chow feeding choice task that is known to be sensitive to dopaminergic manipulations. Tetrabenazine shifted response choice in rats, producing a dose-related decrease in lever pressing and a concomitant increase in chow intake. However, it did not alter food intake or preference in parallel free-feeding choice studies. The effects of tetrabenazine on effort-related choice were reversed by the adenosine A_{2A} antagonist MSX-3 and the antidepressant bupropion. A behaviorally active dose of tetrabenazine decreased extracellular DA in nucleus accumbens and increased expression of DARPP-32 in accumbens medium spiny neurons in a pattern indicative of reduced transmission at both D₁ and D₂ DA receptors. These experiments demonstrate that tetrabenazine, which is used in animal models to produce depression-like effects, can alter effort-related choice behavior. These studies have implications for the development of animal models of the motivational symptoms of depression and related disorders.

Key words: decision making; vigor; motivation; negative symptoms; basal ganglia; DAT inhibitor

Introduction

To survive, organisms must overcome obstacles separating them from motivational stimuli and make effort-related decisions based upon cost/benefit analyses (Salamone and Correa, 2002, 2012). There is considerable interest in characterizing the neural circuitry underlying effort-based processes in animals (Salamone et al., 1997, 2007; Walton et al., 2003; Cagniard et al., 2006; Floresco and Ghods-Sharifi, 2007; Mingote et al., 2008; Hauber and Sommer, 2009; Salamone and Correa, 2012; Nunes et al., 2013a;

Pasquereau and Turner, 2013) and humans (Croxson et al., 2009; Kurniawan et al., 2010; Wardle et al., 2011; Treadway et al., 2012a). Effort-based decision making is studied with tasks offering choices between high effort options leading to highly valued reinforcers versus low effort/low reward options. In animal studies, such tasks include operant procedures offering choices between responding on ratio schedules for preferred reinforcers versus approaching and consuming a less preferred food (Salamone et al., 1991, 2002; Randall et al., 2012), a T-maze barrier crossing task (Salamone et al., 1994; Mott et al., 2009; Pardo et al., 2012), and effort discounting (Floresco et al., 2008; Bardgett et al., 2009). Considerable research has focused on the effort-related functions of dopamine (DA) systems, particularly accumbens DA. Across multiple tasks, low doses of DA antagonists and accumbens DA depletions or antagonism shift choice behavior, decreasing selection of high effort/high reward options, and increasing selection of low effort/low reward choices (Salamone et al., 1994, 1997, 2007; Nowend et al., 2001).

People with depression and related disorders commonly show profound motivational impairments, including psychomotor retardation, anergia, lassitude, and fatigue, which can be highly resistant to treatment (Stahl, 2002; Bella et al., 2010). Tasks measuring effort-based functions have been suggested as potential models for these

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motivational symptoms (Salamone et al., 2006, 2007). Tests of effort-related decision making have been developed in humans (Treadway et al., 2009), and depressed patients show reduced selection of high effort alternatives (Treadway et al., 2012b). The present work investigated the effort-related effects of tetrabenazine, a selective and reversible inhibitor of vesicular monoamine transporter-2 (VMAT-2). Tetrabenazine blocks storage and depletes monoamines, but its greatest impact is upon striatal DA (Pettibone et al., 1984; Tanra et al., 1995). Tetrabenazine is used to treat Huntington's disease, but depressive symptoms including fatigue are major side effects (Frank, 2009, 2010). Moreover, tetrabenazine has frequently been used in studies involving animal models of depression (Preskorn et al., 1984; Kent et al., 1986; Wang et al., 2010). The present studies assessed the effort-related effects of tetrabenazine in rats using the concurrent fixed ratio 5 (FR5) lever-pressing/chow-feeding choice task (Salamone et al., 1991, 2002, 2009). It was hypothesized that low systemic doses and intra-accumbens injections of tetrabenazine would alter choice behavior, decreasing lever pressing but increasing consumption of the concurrently available chow. The adenosine A_{2A} antagonist MSX-3 [(*E*)-phosphoric acid mono-[3-[8-[2-(3-methoxyphenyl)vinyl]-7-methyl-2,6-dioxo-1-prop-2-ynyl-1,2,6,7-tetrahydropurin-3-yl]propyl] ester disodium salt] and the antidepressant bupropion were assessed for their ability to reverse the effects of tetrabenazine. Additional studies determined the effect of tetrabenazine on extracellular DA using microdialysis methods and DA-related signal transduction activity using immunocytochemistry for phosphorylated DARPP-32.

Materials and Methods

Animals

Adult male Sprague Dawley rats (Harlan-Sprague Dawley) were pair housed in a colony maintained at 23°C with 12 h light/dark cycles (lights on at 7:00 h). Rats ($N = 129$) weighed 290–340 g at the beginning of the study and were initially food restricted to 85% of their free-feeding body weight for operant training. Rats were fed supplemental chow to maintain the food restriction throughout the study, given water *ad libitum*, and allowed modest weight gain throughout the experiments. Animal protocols were approved by the University of Connecticut institutional animal care and use committee and followed National Institutes of Health guidelines.

Pharmacological agents

Tetrabenazine [(*R,R*)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-pyrido[2,1-*a*]isoquinolin-2-one] and bupropion [(*RS*)-1-(3-chlorophenyl)-2-*tert*-butylamino-propan-1-ol hydrochloride] were obtained from Tocris Bioscience. Tetrabenazine was dissolved in a 10% dimethyl sulfoxide (DMSO) solution mixed with saline and pH adjusted with 1 N HCl to bring the final solution to pH 3.5. The 10% DMSO solution used to dissolve the tetrabenazine served as the vehicle control. Doses of tetrabenazine used were based on previous data and pilot studies. Bupropion was dissolved in 0.9% saline. MSX-3 was provided by Christa Müller at the Pharmazeutisches Institut, Universität Bonn, in Bonn, Germany (Hockemeyer et al., 2004). MSX-3 (free acid) was dissolved in 0.9% saline and pH was adjusted by titrating with microliter quantities of 1.0 N NaOH until the drug was in solution. The final pH was usually 7.5 ± 0.2 and was not allowed to exceed 7.8. Doses were selected based upon pilot experiments and previous studies; the doses of MSX-3 selected have been shown previously to reverse DA antagonist-induced impairments in FR5 lever pressing and effort-related choice (Farrar et al., 2007; Worden et al., 2009), but did not affect FR5/chow-feeding performance when administered alone (Farrar et al., 2007).

Behavioral procedures

Behavioral sessions were conducted in operant conditioning chambers (28 × 23 × 23 cm; Med Associates). Rats were initially trained to lever press on a continuous reinforcement schedule (30 min sessions for 5 d) reinforced by high carbohydrate 45 mg pellets (Bio-serv) and were then

shifted to the FR5 schedule (30 min sessions 5 d/week) and trained for 5 additional weeks. Rats were then trained on the concurrent FR5/chow-feeding procedure (Salamone et al., 2002; Nunes et al., 2010). Weighed amounts of laboratory chow (5P00 Laboratory Diet; Prolab or RHM 3000; Purina Mills; typically 15–20 g in 3 large pieces) were concurrently available on the floor of the chamber during the FR5 sessions. After the session, rats were immediately removed from the chambers and food intake was determined by weighing the remaining food (including spillage). Rats were trained until they attained stable levels of baseline lever pressing and chow intake (i.e., consistent responding over 1200 lever presses per 30 min; typically 3 weeks), after which time drug testing began. For most baseline days, rats did not receive supplemental feeding; however, over weekends and after drug tests, rats usually received additional chow in the home cage. On baseline and drug treatment days, rats normally consumed all the operant pellets that were delivered from lever pressing during each session. For the food preference study, rats were trained for several weeks in 30 min sessions in which both Bio-serv pellets and laboratory chow were available for consumption. At the end of the session, rats were immediately removed from the chambers and food intake was determined by weighing the remaining food (including spillage).

Surgery

For intracranial injections, rats received bilateral implantation of guide cannulae made with 25 gauge extra-thin-wall stainless steel tubing (Small Parts), which were implanted 1.0 mm dorsal to the target site at the following coordinates: accumbens core (AP +1.6 mm from the bregma, ML ± 1.4 mm from the midline, DV -6.8 mm from the skull surface; incisor bar +5.0 mm above the interaural line); control site 3.0 mm dorsal to the accumbens core (AP +1.6 mm from the bregma, ML +1.4 mm from the midline, DV -3.8 mm from the skull surface; incisor bar +5.0 mm above the interaural line). Animals were anesthetized with injection of a solution (1.0 ml/kg, i.p.) that was prepared by mixing 10.0 ml of 100.0 mg/ml ketamine and 0.75 ml of 20.0 mg/ml xylazine and placed in a stereotaxic device (David Kopf Instruments). For the microdialysis experiment, the tips of the guide cannulae (Bioanalytical Systems) were implanted 2.0 mm dorsal to the accumbens core (AP +2.8 mm, ML -1.4 mm, DV -5.8 mm from bregma). All guide cannulae were secured to the skull by stainless steel screws and cranioplastic cement and a stainless steel stylet was inserted through each guide cannula to insure its integrity. After surgery, animals were allowed to recover for a minimum of 7 d before testing.

Nissl staining for identifying cannula placements

At the completion of behavioral testing in the intracranial injection and microdialysis experiments, each animal was anesthetized with CO₂ and then perfused intracardially with physiological saline followed by a 3.7% formaldehyde solution. The brains were removed and stored in formaldehyde and then sliced with a cryostat in 50 μ m sections, which were mounted on glass microscope slides. After mounting, slides were stained with cresyl violet for microscopic observation by an observer who was unaware of the experimental treatment. Any animal with improper cannulae placement or significant damage around the injection site was excluded from the statistical analyses of behavioral data.

DA microdialysis

On the mornings of sample collection days, dialysis probes (Bioanalytical Systems) were inserted through the microdialysis guide cannulae. Artificial CSF (aCSF; 147.2 mM NaCl, 2.4 mM CaCl₂, 4.0 mM KCl) was continuously perfused through the probe at a rate of 2.0 μ l/min. Neurochemical samples were collected every 30 min in microcentrifuge tubes that contained 2.0 μ l of 70% perchloric acid to prevent oxidation of DA. Twelve samples were collected through the day at an interval of 30 min for each collection tube. Starting 2 h after the initial insertion of the probe, the first 5 samples were collected before the intraperitoneal injection of 0.75 mg/kg tetrabenazine to establish a stable DA level and the last 2 of those baseline samples were used as the statistical baseline. Samples were frozen and analyzed for DA using reverse-phase high-performance liquid chromatography with electrochemical detection (ESA). The electrochemical parameters were as follows: channel 1 = -100 mV, channel

2 = +200 mV, guard cell = +350 mV. Each liter of mobile phase contains 27.5 g sodium phosphate monobasic, 7.0% methanol, 750 μ l of 0.1 M EDTA, and 2200 μ l of 0.4 M sodium octyl sulfate dissolved in deionized ultrapure H₂O with a final pH of 4.5. The flow rate was 1.0 ml/min. DA standards were run before, during, and after the dialysate samples. Probe placements were verified with histological analyses and only probes with placement in the nucleus accumbens core were used for these analyses.

cFos and DARPP-32 immunohistochemical methods

After drug treatments (see below), the animals in Experiments 7–9 were anesthetized with CO₂ and transcardially perfused with 0.9% physiological saline for 5 min, followed by perfusion with 3.7% formaldehyde for 5 min. Brains were fixed for 24 h by immersion in 3.7% formaldehyde and then transferred into a 30% sucrose solution for 48 h at 4°C before brain sectioning. Free floating coronal sections of brains (50 μ m) were serially cut using a Cryostat 9 (Thermo Fisher) and rinsed in 0.01 M phosphate buffer (PBS). To measure the immunoreactivity to phosphorylated DA and c-AMP-regulated phosphoprotein 32 kDa (pDARPP-32), nonspecific binding sites were blocked, and cells were permeabilized in a solution containing 0.1% Triton X-100 (T.X), 10% normal donkey serum (NDS) in PBS for 30 min at room temperature on a rotating platform before primary antibody incubation. pDARPP-32 immunoreactivity was visualized with a polyclonal rabbit antibody for pDARPP-32 phosphorylated at the threonine 34 residue (Thr34, 1:1000; Santa Cruz Biotechnology), or polyclonal rabbit antibody for pDARPP-32 phosphorylated at the threonine 75 residue (Thr75, 1:1000; Santa Cruz Biotechnology). These antibodies were dissolved in solutions that also contained 10% NDS and 0.1% T.X in PBS for 48 h incubation on a rotating shaker at 4°C. After the primary antibody treatment, the sections were rinsed in PBS (3 times for 5 min) and incubated in the secondary antibody, anti-rabbit HRP conjugate envision plus (DAKO) for 2 h on a rotating shaker at room temperature. Finally, sections were washed and rinsed for 3–5 min in 3,3'-diaminobenzidine chromagen. The sections were then mounted to gelatin-coated slides, air dried, and coverslipped using Cytoseal 60 (Thermo Scientific) as a mounting medium. The tissue was then examined by light microscopy. The processing of the c-Fos tissue was similar to the procedures described for pDARPP-32, with the main difference being the blocking step, which consisted of a solution of 0.3% H₂O₂ and 1% bovine serum albumin, and the use of a c-Fos specific primary antibody (rabbit polyclonal anti c-Fos, 1:5000; Calbiochem).

Quantification of DARPP-32 and c-Fos-positive cells

Quantification of the number of cells that express immunoreactivity for c-Fos in nucleus accumbens core and pDARPP-32(Thr34) and pDARPP-32(Thr75) in the nucleus accumbens core and shell was performed by photographing the sections with a 20 \times (0.125 mm²/field) objective (Eclipse E600; Nikon) upright microscope equipped with an Insight Spot digital camera (Diagnostic Instruments). Images of the regions of interest were magnified at 20 \times and captured digitally using SPOT software. Cells that were positively labeled for pDARPP-32(Thr34), pDARPP-32(Thr75), or c-Fos were quantified with ImageJ software (version 1.42) and a macro written to automate particle counting within the region of interest. The size of the region of interest was 1000 \times 1000 μ m. For each animal, cell counts were at levels that correspond to 0.70–1.70 mm anterior to bregma (Paxinos and Watson, 1997) bilaterally from at least three sections and counts were averaged across slides and sections.

Immunofluorescence double-labeling studies of DARPP-32, substance P, and enkephalin

Free-floating coronal sections of brains (50 μ m) were serially cut using a cryostat and rinsed in 0.01 M PBS. To measure the immunoreactivity to pDARPP-32, nonspecific binding sites were blocked and cells were permeabilized in a solution containing 0.1% T.X and 10% NDS in PBS for 30 min at room temperature on a rotating platform before primary antibody incubation. pDARPP-32 immunoreactivity was visualized with a polyclonal rabbit antibody for pDARPP-32(Thr34) (1:500; Santa Cruz Biotechnology) or polyclonal rabbit antibody for pDARPP-32(Thr75) (1:500; Santa Cruz Biotechnology). The different forms of pDARPP-32 were double labeled with primary antibodies for substance P (goat poly-

clonal, 1:400; Santa Cruz Biotechnology) or enkephalin (mouse monoclonal, 1:400; Millipore). These antibodies were dissolved in solutions that also contained 10% NDS and 0.1% T.X in PBS for a 48 h incubation on a rotating shaker at 4°C. After the primary antibody treatment, the sections were rinsed in PBS (3 times for 5 min) and incubated in the secondary antibody solution containing donkey anti-rabbit Alexa Fluor 488 (1:500; Life Technologies) and donkey anti-goat Alexa Fluor 594 (1:500; Life Technologies) or donkey anti-mouse Alexa Fluor 594 (1:500; Life Technologies). These antibodies were dissolved in solutions that also contained 10% NDS and 0.1% T.X in PBS for a 2 h incubation on a rotating shaker at 22°C. The sections were then mounted to gelatin-coated slides, air dried, and coverslipped using ProLong Gold antifade medium (Life Technologies). Immunofluorescence staining was visualized for high-resolution observation on an Axio Imager M2 upright fluorescent microscope (Carl Zeiss), photographed with a Hamamatsu ORCA-R2 C10600 digital camera, and analyzed with Stereo Investigator software (MicroBrightField).

Behavioral experiments

Rats were trained on the concurrent FR5/chow-feeding procedure (as described above) before testing began and each experiment used different groups of rats. Experiments 1–4 used a within-groups design, with each rat receiving intraperitoneal drug treatments in their particular experiment in a randomly varied order (one treatment per week, with none of the treatment sequences repeated across different animals in the same experiment). Baseline (i.e., nondrug) sessions were conducted an additional 4 d per week. Behavioral measures included both the number of lever presses and the amount of freely available laboratory chow that was consumed. The specific treatments and testing times for each experiment are listed below. Experiment 5 involved intracranial injections of tetrabenazine; this experiment was a between-groups design, with each animal receiving only one treatment.

Experiment 1: Effects of systemic administration of the VMAT-2 inhibitor tetrabenazine on the concurrent FR5/chow-feeding procedure. Rats were trained until stable baseline performance was achieved (i.e., lever presses consistently > 1200 per session). During the experiment, all animals ($n = 8$) received intraperitoneal injections of the following treatments: 10% DMSO vehicle and 0.25, 0.5, 0.75, and 1.0 mg/kg tetrabenazine. Injections were given 90 min before the beginning of the testing session.

Experiment 2: Effects of systemic administration of tetrabenazine on free food intake and preference. Rats were trained the same two foods used in the operant behavior experiments (Bio-serv pellets and laboratory chow) until stable baseline performance was achieved (i.e., food consumption > 10 g). During the experiment, all animals ($n = 8$) received intraperitoneal injections of the following treatments: 10% DMSO vehicle and 0.25, 0.5, 0.75, and 1.0 mg/kg tetrabenazine. Injections were given 90 min before the beginning of the testing session.

Experiment 3: Effects of systemic administration of tetrabenazine on the concurrent FR5/chow-feeding procedure: reversal with MSX-3. Rats were trained as described above, and then all animals ($n = 8$) received intraperitoneal injections of the following combined treatments: 10% DMSO vehicle (90 min before testing) plus saline vehicle (20 min before testing), 0.75 mg/kg tetrabenazine (90 min) plus saline vehicle (20 min), 0.75 mg/kg tetrabenazine (90 min) plus 0.5 mg/kg MSX-3 (20 min), 0.75 mg/kg tetrabenazine (90 min) plus 1.0 mg/kg MSX-3 (20 min), and 0.75 mg/kg tetrabenazine (90 min) plus 2.0 mg/kg MSX-3 (20 min).

Experiment 4: Effects of systemic administration of tetrabenazine on the concurrent FR5/chow-feeding procedure: reversal with bupropion. Rats were trained as described above, and then all animals ($n = 11$) received intraperitoneal injections of the following combined treatments: 10% DMSO vehicle (90 min before testing) plus saline vehicle (30 min before testing), 0.75 mg/kg tetrabenazine (90 min) plus saline vehicle (30 min), 0.75 mg/kg tetrabenazine (90 min) plus 5.0 mg/kg bupropion (30 min), 0.75 mg/kg tetrabenazine (90 min) plus 10.0 mg/kg bupropion (30 min), and 0.75 mg/kg tetrabenazine (90 min) plus 15.0 mg/kg bupropion (20 min).

Experiment 5: Behavioral effects of tetrabenazine locally administered into the nucleus accumbens core. All animals ($N = 24$) were trained until a stable baseline performance was achieved (i.e., lever presses > 1200). Rats

were then implanted with bilateral cannulae targeted at the accumbens core ($n = 19$) or a medial neostriatal control site dorsal to the core ($n = 5$). After recovery from surgery and retraining, rats with accumbens core placements received bilateral injections of vehicle ($n = 7$) or 10.0 μg ($n = 5$) or 20.0 μg of tetrabenazine ($n = 7$). Animals with dorsal control placements received 20.0 μg of tetrabenazine. All injections were given in a total volume of 0.5 μl per side and rats were tested 15 min after drug infusion. This experiment (and Experiment 6) focused on nucleus accumbens core because of previous research showing that the accumbens core is the most effective striatal site at which DA depletion and inactivation produce effects on effort-related choice behavior (Cousins et al., 1993; Sokolowski and Salamone, 1998; Ghods-Sharifi and Floresco, 2010); furthermore, this is a highly effective site for the actions of D_2 antagonists (Farrar et al., 2010) and adenosine A_{2A} receptor agonists and antagonists (Font et al., 2008; Mingote et al., 2008; Farrar et al., 2010) on effort-related functions.

Neurochemical experiments

Neurochemical experiments were conducted to determine the effects of a behaviorally active dose of tetrabenazine (0.75 mg/kg; see Experiments 3–4 above) on extracellular DA and DA-related markers of signal transduction (c-Fos and pDARPP-32).

Experiment 6: Effect of tetrabenazine on extracellular DA in nucleus accumbens. Rats were implanted with dialysis probes in nucleus accumbens core as described above. On the test day, they received intraperitoneal injections of either vehicle ($n = 5$) or 0.75 mg/kg tetrabenazine ($n = 6$).

Experiments 7 and 8: Effect of tetrabenazine on cFos and pDARPP-32 expression in nucleus accumbens: reversal with MSX-3. On the test day, untrained rats received intraperitoneal injections of vehicle ($n = 16$), 0.75 mg/kg tetrabenazine ($n = 16$), or 0.75 mg/kg tetrabenazine plus 2.0 mg/kg MSX-3 ($n = 16$). Of these animals, half in each condition were used for the cFos experiment and were killed 90 min after injection, and the other half were used for the pDARPP-32 experiment and killed 45 min after injection. Immunocytochemical methods were used to analyze tissue sections as described above.

Experiment 9: Effect of tetrabenazine on pDARPP-32(Thr34) and pDARPP-32(Thr75) expression in substance-P- and enkephalin-positive neurons in nucleus accumbens: immunofluorescence double labeling. Rats received intraperitoneal injections of 0.75 mg/kg tetrabenazine ($n = 6$). Immunofluorescence double-labeling methods were used to analyze tissue sections as described above to determine the peptides that coexpress with neurons that express pDARPP-32(Thr34) and pDARPP-32(Thr75).

Statistical analyses

In Experiments 1, 3, and 4, lever presses and gram quantity of chow intake from the 30 min sessions were analyzed with repeated-measures ANOVA. For the food preference study (Experiment 2), the total quantity of Bio-Serv pellets and chow were analyzed with factorial ANOVA. Experiment 5 was analyzed using between-groups ANOVA. In Experiments 1 and 5, nonorthogonal planned comparisons using the overall error term were used to compare each treatment with the vehicle control condition (Keppel, 1991). For these comparisons, the α level was kept at 0.05 because the number of comparisons was restricted to the number of treatments minus one. In Experiments 3 and 4, each condition that combined tetrabenazine plus MSX-3 or bupropion was compared with the tetrabenazine/vehicle condition using nonorthogonal planned comparisons. Changes in extracellular DA levels in the microdialysis experiment were calculated as the percentage change from baseline, with the mean of the two samples immediately preceding the lever pressing session serving as the 100% baseline level. A factorial ANOVA with repeated measures on the sample factor was used to test for differences in extracellular levels of DA. The raw DA levels of the baseline samples were analyzed using t test to verify that the baseline DA levels were not different between conditions. For the cFos immunohistochemistry experiment, a between-subjects ANOVA was used and planned comparisons were used to determine pairwise differences between treatments. For Experiment 8, data for each phosphorylated form of DARPP-32 (i.e., Thr34 and Thr75) were analyzed separately with a brain area (core vs shell) \times drug treat-

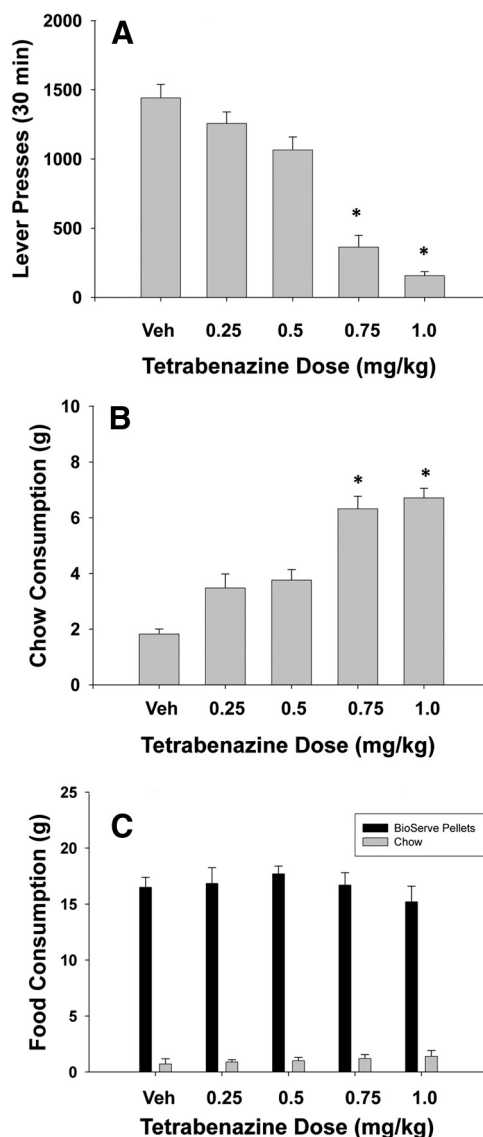


Figure 1. Behavioral effects of tetrabenazine. **A**, Mean (\pm SEM) number of lever presses after treatment with vehicle and various doses of tetrabenazine ($n = 8$). **B**, Mean (\pm SEM) intake of laboratory chow (in grams) after treatment with vehicle and various doses of tetrabenazine. * $p < 0.05$, different from vehicle, planned comparison. **C**, Mean (\pm SEM) intake of Bio-serv pellets and laboratory chow (in grams) after treatment with vehicle and various doses of tetrabenazine ($n = 8$).

ment factorial ANOVA, with repeated measures on the brain area factor. When there was a significant area \times treatment interaction, these analyses were followed by separate analyses of each area and post hoc comparisons with the Tukey test ($\alpha = 0.05$).

Results

Experiment 1: Effects of systemic administration of the VMAT-2 inhibitor tetrabenazine on the concurrent FR5/ chow-feeding procedure

Systemic administration of tetrabenazine significantly decreased lever pressing and produced a concurrent increase in the consumption of the freely available laboratory chow, as shown in Figure 1, A and B. ANOVA revealed a significant effect of dose on lever pressing ($F_{(4,28)} = 45.9, p < 0.001$). There was also an overall significant effect of drug treatment on chow intake ($F_{(4,28)} = 33.8, p < 0.001$). Planned comparisons were performed and showed that the two highest doses of tetrabenazine significantly decreased lever pressing

and increased the consumption of the freely available laboratory chow relative to control ($p < 0.05$).

Experiment 2: Effects of systemic administration of tetrabenazine on free food intake and preference

The results of Experiment 2 are shown in Figure 1C. There was a significant difference between food type consumed, with rats preferring the Bio-serv pellets over the standard laboratory chow ($F_{(1,14)} = 661$; $p < 0.001$). However, there was no significant effect of drug treatment on food intake ($p > 0.05$) and no significant drug treatment \times food type interaction ($p > 0.05$).

Experiments 3 and 4: Effects of systemic administration of the tetrabenazine on the concurrent FR5/chow-feeding procedure: reversal with MSX-3 and bupropion

The results of Experiment 3 are shown in Figure 2, A and B. MSX-3 was able to attenuate the behavioral effects of tetrabenazine. There was an overall significant effect of drug treatment on lever pressing ($F_{(4,28)} = 26.8$, $p < 0.001$). There was also an overall significant effect of drug treatment on chow intake ($F_{(4,28)} = 40.5$, $p < 0.001$). Planned comparisons were performed and showed that tetrabenazine suppressed lever pressing and increased chow intake and that all doses of MSX-3 were able to attenuate the effects of tetrabenazine both on lever pressing and consumption of the freely available laboratory chow relative to the tetrabenazine alone condition ($p < 0.05$).

As shown in Figure 2, C and D, the antidepressant bupropion was able to attenuate the behavioral effects of tetrabenazine. There was an overall significant effect of drug treatment on lever pressing ($F_{(4,40)} = 19.4$, $p < 0.001$) and also an overall significant effect of drug treatment on chow intake ($F_{(4,40)} = 46.3$, $p < 0.001$). Planned comparisons showed that, as in the previous two experiments, 0.75 mg/kg tetrabenazine decreased lever pressing and increased chow intake. In addition, the two highest doses of bupropion significantly increased lever pressing and also decreased the consumption of the freely available laboratory chow relative to the tetrabenazine condition ($p < 0.05$).

Experiment 5: Effects of tetrabenazine locally administered into the nucleus accumbens core on the concurrent FR5/chow-feeding procedure

Results of Experiment 5 are shown in Figure 3. There was an overall significant effect of drug treatment on lever pressing ($F_{(3,23)} = 16.9$, $p < 0.001$) and also on chow intake ($F_{(3,23)} = 22.2$, $p < 0.001$). Planned comparisons showed that accumbens core injections of the highest dose of tetrabenazine produced a significant effect on lever pressing and chow consumption compared with vehicle ($p < 0.05$). Injection of 20.0 μ g of tetrabenazine into

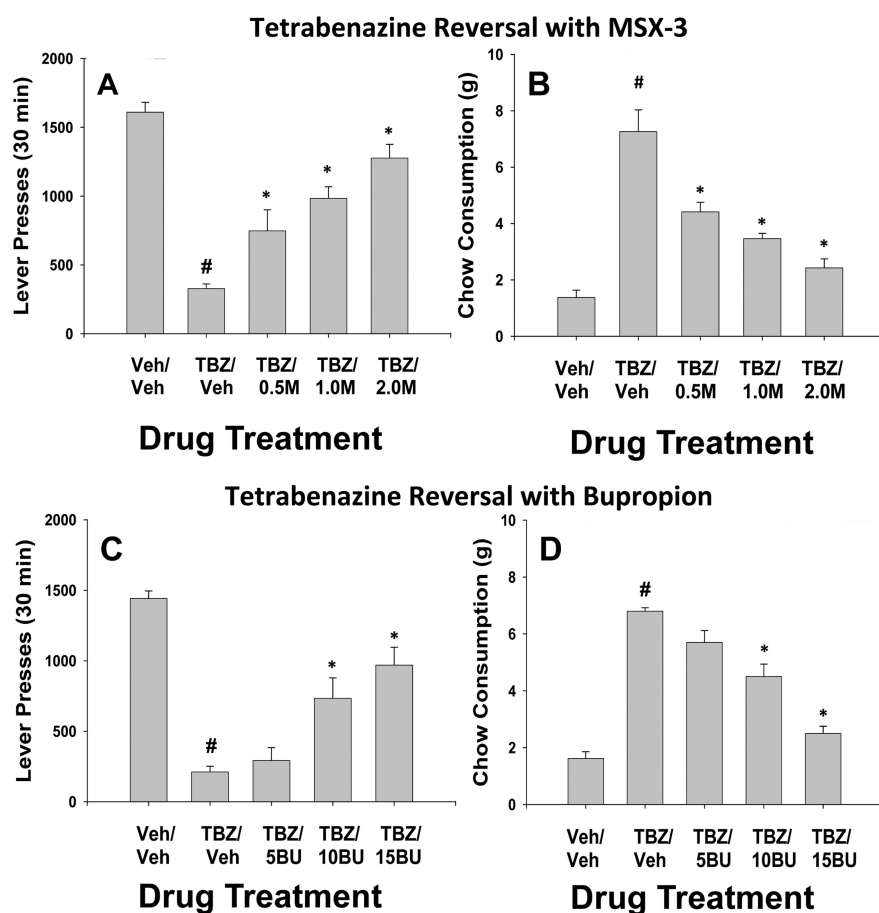


Figure 2. The effects of the adenosine A_{2A} antagonist MSX-3 and the antidepressant bupropion on tetrabenazine-induced changes in performance on the concurrent lever pressing/chow-feeding procedure. **A, B**, Tetrabenazine and MSX-3. Rats ($n = 8$) received intraperitoneal injections of vehicle plus vehicle (Veh/Veh), 0.75 mg/kg tetrabenazine plus vehicle (TBZ/Veh), or tetrabenazine plus 0.25, 0.5, 1.0, or 2.0 mg/kg doses of MSX-3 (M). **A**, Mean (\pm SEM) number of lever presses (FR5 schedule) during the 30 min session. **B**, Mean (\pm SEM) gram quantity of chow intake. **C, D**, Tetrabenazine and bupropion. Rats ($n = 11$) received intraperitoneal injections of vehicle plus vehicle (Veh/Veh), 0.75 mg/kg tetrabenazine plus vehicle (TBZ/Veh), or tetrabenazine plus 5.0, 10.0, or 15.0 mg/kg doses of bupropion (BU). **C**, Mean (\pm SEM) number of lever presses (FR5 schedule) during the 30 min session. **D**, Mean (\pm SEM) gram quantity of chow intake. # $p < 0.05$, tetrabenazine plus vehicle significantly differed from vehicle/vehicle; * $p < 0.05$, significantly different from tetrabenazine plus vehicle.

the neostriatal control site dorsal to the accumbens core did not alter lever pressing or chow intake compared with vehicle, but this group did differ on both measures from the rats that received the same dose into the nucleus accumbens ($p < 0.05$, Tukey test).

Experiment 6: Effect of tetrabenazine on extracellular DA in nucleus accumbens

Figure 4A summarizes the results of the microdialysis experiment. The vehicle ($n = 5$) and 0.75 mg/kg tetrabenazine ($n = 6$) groups did not differ in terms of baseline levels of extracellular DA (mean \pm SEM DA expressed as picograms/sample; vehicle: 27.5 ± 8.1 ; tetrabenazine: 21.6 ± 4.5 ; $t = 0.55$, $df = 9$, $p > 0.5$, NS). Factorial ANOVA across all 9 samples (Fig. 4A) demonstrated that there was a significant effect of drug treatment ($F_{(1,9)} = 8.1$, $p < 0.05$), a significant difference across samples ($F_{(8,72)} = 3.53$, $p < 0.05$), and a significant treatment \times sample interaction ($F_{(8,72)} = 2.3$, $p < 0.05$). Separate analyses of each treatment group showed that there was no significant change over samples in the vehicle group ($F_{(8,32)} = 0.192$, $p > 0.9$, NS), but there was a significant change in DA levels across samples for the tetrabenazine group ($F_{(8,40)} = 5.81$, $p < 0.001$). Planned comparisons showed that animals injected with 0.75 mg/kg tetrabenazine had

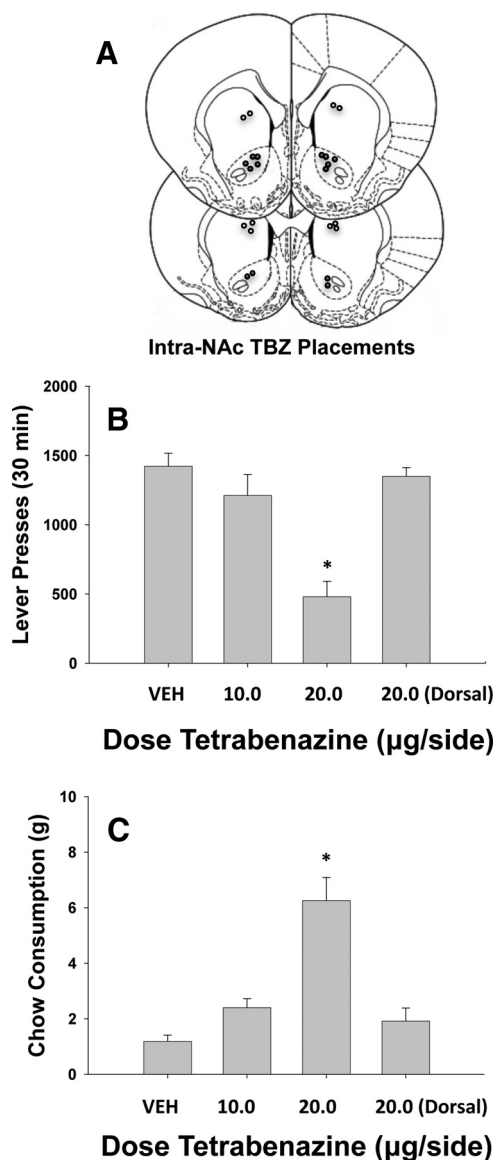


Figure 3. Intracranial administration of tetrabenazine. **A**, Placements of cannulae in nucleus accumbens core (filled circles) and the dorsal control site (open circles) in rats that received the 20.0 μg dose of tetrabenazine. **B**, Mean (± SEM) number of lever presses after treatment with either vehicle ($n = 7$), 10.0 μg ($n = 5$), or 20.0 μg ($n = 7$) per side of tetrabenazine injected into nucleus accumbens core or 20.0 μg per side injected into the dorsal control site ($n = 5$). **C**, Mean (± SEM) intake of laboratory chow (in grams) after treatment with vehicle, 10.0 μg or 20.0 μg per side of tetrabenazine injected into nucleus accumbens core, or 20.0 μg per side injected into the dorsal control site. * $p < 0.05$, different from vehicle, planned comparison.

significantly lower levels of extracellular DA in samples D4–D7 relative to the last baseline sample ($p < 0.05$).

Experiments 7–9: Tetrabenazine affects the DA-related signal transduction markers cFos and DARPP-32

The results of immunocytochemistry experiments are shown in Figure 4, *B–D*, and Figure 5. There was an overall effect of drug treatment on the number of cFos positive cell in nucleus accumbens core ($F_{(2,23)} = 73.0$, $p < 0.001$; Fig. 4*B*). Planned comparisons showed that tetrabenazine increased cFos-positive cells counts relative to vehicle alone ($p < 0.05$) and that the combination of tetrabenazine plus MSX-3 differed significantly from tetrabenazine plus vehicle ($p < 0.05$). In Experiment 8, analyses of pDARPP-32(Thr34) immunoreactivity (Fig. 4*C*) showed that

there was no overall difference between core and shell ($F_{(1,21)} = 0.5$, NS), but there was an overall effect of drug treatment on the number of pDARPP-32(Thr34)-positive cells ($F_{(2,21)} = 87.72$, $p < 0.05$) and a significant brain area × drug treatment interaction ($F_{(2,21)} = 6.18$, $p < 0.05$). Separate ANOVAs of core and shell revealed that the drug treatment effects were significant in both areas ($p < 0.05$) and planned comparisons revealed that tetrabenazine produced a significant increase in pDARPP-32(Thr34) expression ($p < 0.05$) in both areas, which was suppressed by coadministration of MSX-3 ($p < 0.05$). However, the source of the interaction was that MSX-3 produced a greater suppression of tetrabenazine-induced expression of pDARPP-32(Thr34) in the core relative to shell ($p < 0.05$). There was also an overall effect of drug treatment on the number of pDARPP-32(Thr75)-positive cells ($F_{(2,21)} = 72.5$, $p < 0.05$; Fig. 4*D*), but no significant core versus shell difference ($F_{(1,21)} = 1.5$, NS) and no brain area × treatment interaction ($F_{(2,21)} = 1.8$, NS). Collapsed across both regions, tetrabenazine produced an overall increase in pDARPP-32(Thr75) expression ($p < 0.05$), but MSX-3 failed to suppress the tetrabenazine-induced increase in pDARPP-32(Thr75)-positive cells. Figure 5 shows the results of the immunofluorescence double-labeling study. In animals treated with 0.75 mg/kg tetrabenazine, pDARPP-32(Thr34) was coexpressed with enkephalin, but not substance P, whereas pDARPP-32(Thr75) was coexpressed with substance P, but not enkephalin. Together with the results of the single-labeling experiment (Fig. 4*B,C*), this pattern of results is consistent with a reduction of D₁ and D₂ receptor signaling induced by tetrabenazine.

Discussion

These experiments assessed the effort-related motivational effects of the VMAT-2 inhibitor tetrabenazine. Animals show robust activation in the initiation and maintenance of motivated behavior (Salamone and Correa, 2002, 2012; Berridge and Robinson, 2003; Robbins and Everitt, 2007; Nicola, 2010; McGinty et al., 2013) and demonstrate substantial and persistent work output in their instrumental actions. Moreover, they frequently make effort-related decisions, allocating behavioral resources in relation to the motivational value of stimuli and the effort required to obtain them (Salamone and Correa, 2012). The present experiments used the FR5/chow-feeding task as a measure of effort-related choice behavior (Salamone et al., 1991, 1997; Nunes et al., 2010). This task is sensitive to the effects of D₁ or D₂ antagonism and accumbens DA depletions (Salamone et al., 1991, 2002; Cousins et al., 1994; Nowend et al., 2001; Sink et al., 2008; Farrar et al., 2010). Furthermore, the effects of interference with DA transmission on this task are not due to changes in appetite, food intake, or preference (Salamone et al., 1991; Koch et al., 2000) and do not resemble the effects of reinforcer devaluation by prefeeding (Salamone et al., 1991) or appetite suppressant drugs (Cousins et al., 1994; Salamone et al., 2002; Sink et al., 2008). As shown above, tetrabenazine shifted choice behavior, decreasing lever pressing but increasing consumption of the concurrently available chow. In a parallel experiment, the same doses of tetrabenazine had no effect on food intake or preference for high carbohydrate pellets over chow. Therefore, tetrabenazine-induced shifts in effort-related choice were not due to changes in primary food motivation, the unconditioned reinforcing properties of food, or food preference. Although tetrabenazine exerted a selective effect on the tendency to work for food by lever pressing, tetrabenazine-treated rats remained directed toward food acquisition and consumption and selected an alternative path to obtain food (i.e., approach/consumption of the concurrently available

chow). This conclusion is consistent with preliminary studies demonstrating that tetrabenazine also reduced selection of the high effort/high reward option in rats tested on a T-maze barrier choice task (Yohn et al., 2012) and a progressive ratio/chow feeding choice procedure (Salamone et al., 2012). Injections of tetrabenazine into accumbens core also reduced FR5 lever pressing and increased chow intake (Fig. 3), whereas injections into a medial neostriatal control site dorsal to accumbens were ineffective. This is consistent with previous studies linking effort-related choice behavior to accumbens DA (Salamone et al., 1991; Cousins et al., 1993; Nowend et al., 2001; Farrar et al., 2010; Mai et al., 2012; Trifilieff et al., 2013).

Tests of effort-related choice behavior may have utility as preclinical models of motivational symptoms such as psychomotor retardation, anergia, and fatigue, which are seen in depression and other disorders (Salamone et al., 2006, 2007, 2010; Salamone and Correa, 2012). This idea is consistent with human studies of effort-related decision making showing that decreased selection of high effort/high reward options is seen in patients with major depression (Treadway et al., 2012b) and also in schizophrenics with a preponderance of negative symptoms (Gold et al., 2013). Because tetrabenazine produces depressive symptoms including psychomotor slowing and fatigue in human patients (Frank, 2009; Guay, 2010; Chen et al., 2012), the adenosine A_{2A} antagonist MSX-3 and the catecholamine uptake blocker bupropion were assessed for their ability to reverse the behavioral effects of tetrabenazine. Adenosine A_{2A} antagonists produce behavioral effects in animals that are consistent with antidepressant actions (Hodgson et al., 2009; Hanff et al., 2010), and bupropion (Wellbutrin) is a widely used antidepressant drug (Milea et al., 2010) that can produce antidepressant-like effects in rodent tasks such as the forced swim and tail suspension tests (Bourin et al., 2005; Kitamura et al., 2010). MSX-3 fully reversed the effects of tetrabenazine on FR5/chow-feeding choice performance, which is consistent with research demonstrating that adenosine A_{2A} antagonists reverse the effects of DA D_2 family antagonists on effort-related choice behavior (Farrar et al., 2007; Mott et al., 2009; Salamone et al., 2009; Worden et al., 2009; Nunes et al., 2010; Santerre et al., 2012). Bupropion, a catecholamine uptake blocker that elevates extracellular DA and norepinephrine (Hudson et al., 2012), also reversed the effort-related effects of tetrabenazine. It is not clear which catecholamine mediates this action, but there is little evidence implicating norepinephrine in effort-related choice and considerable evidence supporting a role for DA (Salamone et al., 2007). Nevertheless, in view of the

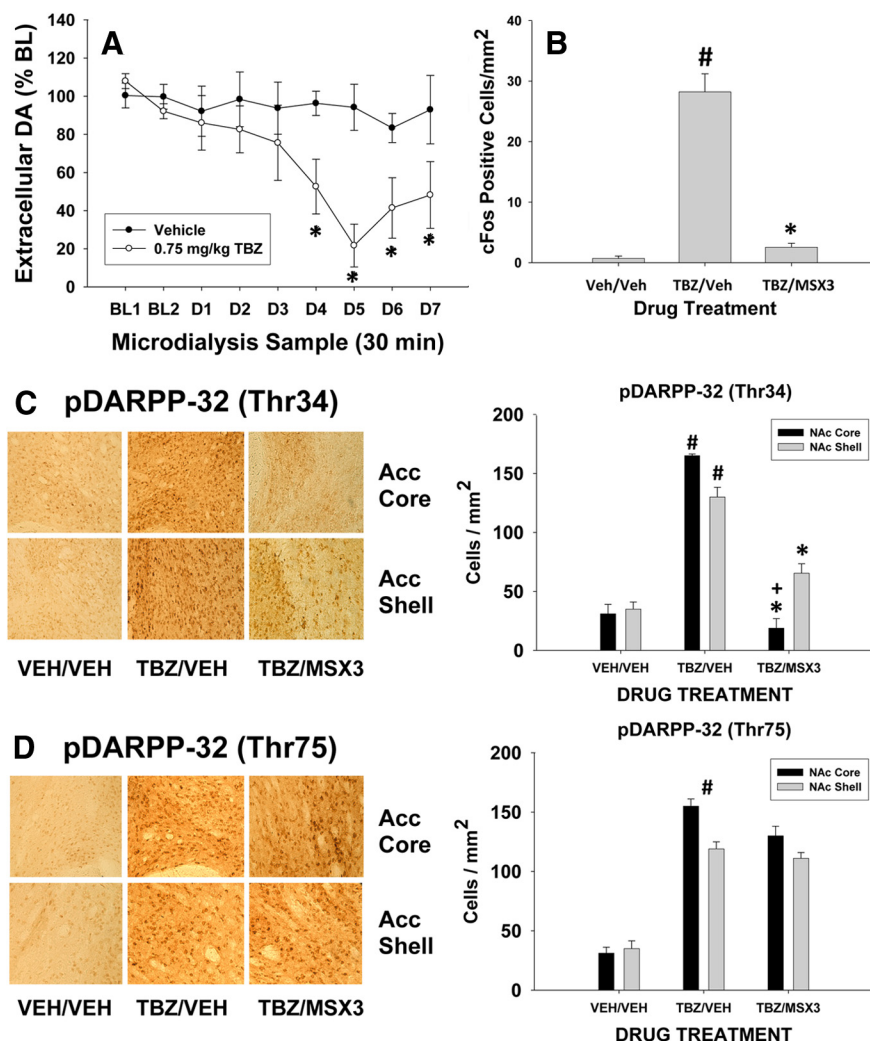


Figure 4. Neurochemical effects of tetrabenazine. **A**, Microdialysis data showing the effect of 0.75 mg/kg tetrabenazine on mean (\pm SEM) extracellular DA (expressed as percentage of baseline) in nucleus accumbens core. Samples (30 min) were collected during the baseline period (BL1 and BL2) and for the 7 samples after the injection of either tetrabenazine ($n = 6$) or vehicle ($n = 5$) (D1–D7). * $p < 0.05$, different from last baseline sample in the tetrabenazine group. **B**, Expression of c-Fos immunoreactivity in nucleus accumbens core. Mean (\pm SEM) number of c-Fos-positive cells in the accumbens and core after injection of vehicle plus vehicle (Veh/Veh; $n = 8$), 0.75 mg/kg tetrabenazine plus vehicle (TBZ/Veh; $n = 8$), or tetrabenazine plus the 2.0 mg/kg dose of MSX-3 ($n = 8$). # $p < 0.05$, tetrabenazine plus vehicle significantly differed from vehicle/vehicle; * $p < 0.05$, significantly different from tetrabenazine plus vehicle. **C**, Expression of pDARPP-32(Thr34) immunoreactivity in nucleus accumbens core and shell after injection of vehicle plus vehicle (Veh/Veh; $n = 8$), 0.75 mg/kg tetrabenazine plus vehicle (TBZ/Veh; $n = 8$), or tetrabenazine plus the 2.0 mg/kg dose of MSX-3 ($n = 8$). Left, Photomicrographs of individual animals. Right, Mean \pm SEM number of pDARPP-32(Thr34)-positive cells. # $p < 0.05$, tetrabenazine plus vehicle significantly differed from vehicle/vehicle; * $p < 0.05$, significantly different from tetrabenazine plus vehicle; + TBZ plus MSX-3 in core significantly differed from TBZ plus MSX-3 in shell. **D**, Expression of pDARPP-32(Thr75) immunoreactivity in nucleus accumbens core and shell after injection of vehicle plus vehicle (Veh/Veh; $n = 8$), 0.75 mg/kg tetrabenazine plus vehicle (TBZ/Veh; $n = 8$), or tetrabenazine plus the 2.0 mg/kg dose of MSX-3 ($n = 8$). Left, Photomicrographs of individual animals. Right, Mean \pm SEM number of pDARPP-32(Thr75) positive cells. #Tetrabenazine plus vehicle significantly differed from vehicle/vehicle across both core and shell.

known antidepressant actions of bupropion in humans, these results validate the hypothesis that tests of effort-related choice behavior can be used to assess some of the motivational effects of antidepressant drugs. Furthermore, these results are consistent with clinical data indicating that bupropion is relatively effective for treating psychomotor retardation and fatigue symptoms of depression (Fabre et al., 1983; Pae et al., 2007) and can be more effective than other antidepressants, including 5-HT uptake blockers, for treating motivational dysfunction in depressed patients (Papakostas et al., 2006).

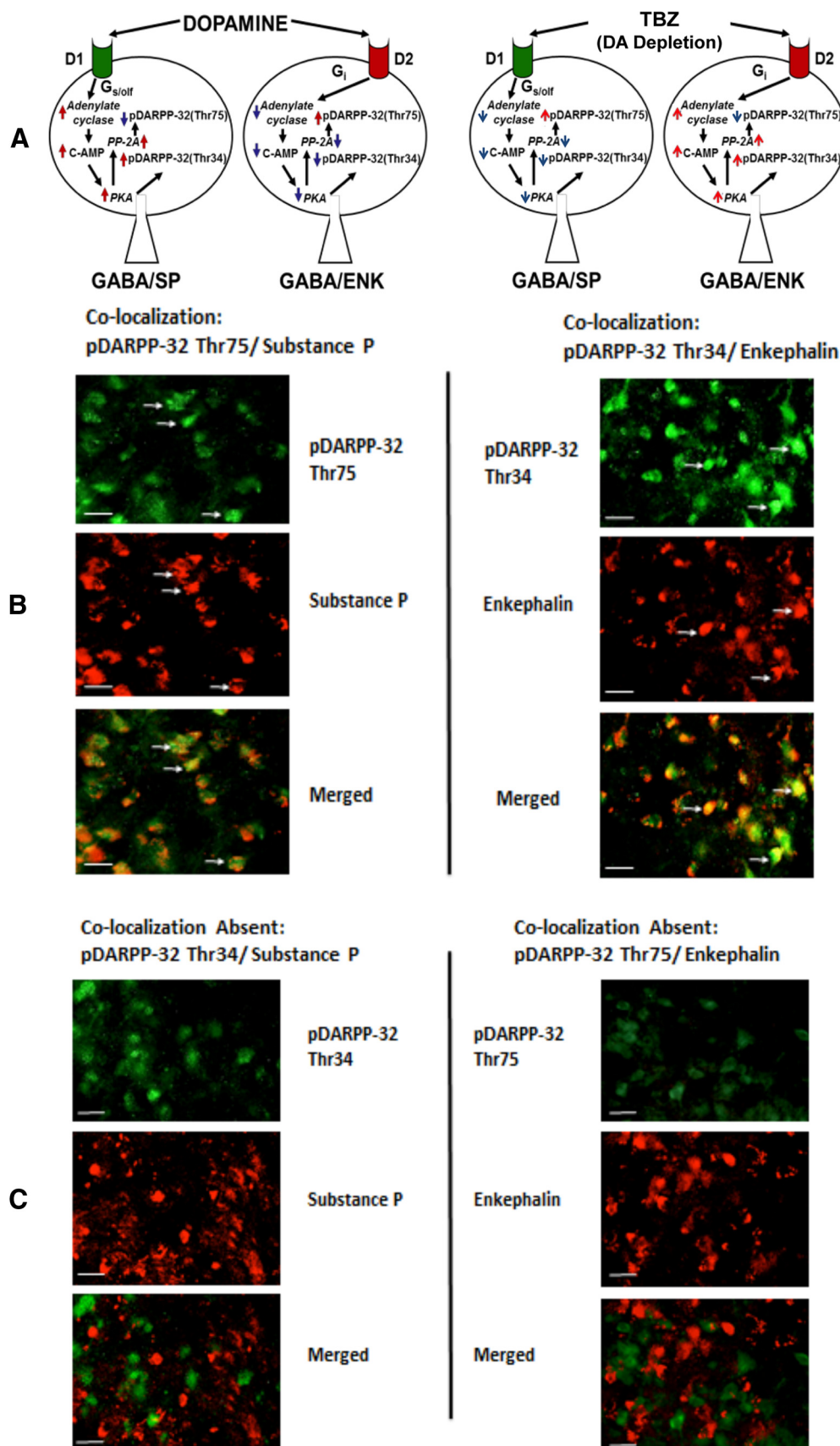


Figure 5. *A*, Left, Diagram showing effect of DA on DARPP-32 phosphorylation (for details, see Svenningsson et al., 2004; Bateup et al., 2008; Yger and Girault, 2011). D₁ receptor stimulation increases c-AMP production and protein kinase A (PKA) activity, which phosphorylates DARPP-32 to yield pDARPP-32(Thr34). D₂ receptor stimulation decreases c-AMP production and protein kinase A activity, which decreases the dephosphorylation of pDARPP-32(Thr75) by protein phosphatase 2A (PP-2A) and therefore increases pDARPP-32(Thr75) expression. Right, Tetrabenazine, which depletes DA, was hypothesized to have the opposite effect of DA, increasing pDARPP-32(Thr75) in substance-P-positive neurons and pDARPP-32(Thr34) in (Figure legend continues.)

Tetrabenazine substantially reduced extracellular DA in accumbens core as measured by microdialysis and also affected DA-related signal transduction in a manner consistent with reduced accumbens D₁ and D₂ receptor transmission. Tetrabenazine increased cFos immunoreactivity in accumbens core and shell, which is consistent with a reduction in D₂ transmission (Robertson et al., 1992; Santerre et al., 2012). Furthermore, immunocytochemistry of different forms of phosphorylated DARPP-32 indicated that 0.75 mg/kg tetrabenazine significantly increased accumbal expression of both pDARPP-32(Thr34) and pDARPP-32(Thr75). Previous results suggest that tetrabenazine-induced increases in pDARPP-32(Thr75) would reflect reduced transmission at DA D₁ family receptors, whereas the increase in pDARPP-32(Thr34) would mark reduced transmission at DA D₂ family receptors (Svenningsson et al., 2004; Bateup et al., 2008; Yger and Girault, 2011; Santerre et al., 2012). These DA receptors are largely localized on separate populations of medium spiny neurons, so immunofluorescence double-labeling studies for both forms of pDARPP-32 were conducted to determine whether there was coexpression with either substance P (marking D₁-receptor-containing cells) or enkephalin (marking D₂-receptor-containing cells; Segovia et al., 2012). These double-labeling studies confirmed that, in tetrabenazine-treated rats, pDARPP-32(Thr75) expression was in substance-P-positive cells, whereas pDARPP-32(Thr34) expression was in enkephalin-positive cells. Interestingly, MSX-3 attenuated the effects of tetrabenazine on pDARPP-32(Thr34) expression, but not pDARPP-32(Thr75) expression. This is consistent with studies showing that adenosine A_{2A} receptors are colocalized with D₂ receptors on enkephalin-positive neurons, but not with D₁ receptors on substance-P-positive neurons (Svenningsson et al., 1999), and that A_{2A} and D₂ receptors can form heteromers and interact via convergence onto c-AMP signal transduction cascades (Ferré et al., 2008). The suppression of tetrabenazine-induced increases in pDARPP-32(Thr34) expression by MSX-3 was greater in the core versus the shell, which may be due to a lower level of adenosine A_{2A} receptor expression in the shell (Rosin et al., 1998; Ishiwari et al., 2007).

By inhibiting VMAT-2, tetrabenazine affects monoamine storage, but studies indicate that the greatest effects are on striatal DA. A study of postmortem tissue of humans receiving clinical doses of tetrabenazine reported that the only statistically significant depletions were DA in the caudate, norepinephrine in the amygdala, and norepinephrine and DA in the hippocampus (Guay, 2010). Pettibone et al. (1984) showed that 1.0 mg/kg tetrabenazine reduced striatal DA in rats by ~75% while reducing 5-HT and norepinephrine by ~15–30%, and observed that a dose of 10.0 mg/kg tetrabenazine was needed to reduce 5-HT as much as 1.0 mg/kg depleted striatal DA. Similar results were shown by Tanra et al. (1995), who reported that 1.0 mg/kg tetrabenazine reduced striatal DA in rats by 57%, whereas with 5-HT, there were no significant reductions in frontal cortex, striatum, or hippocampus and only a 20% reduction in hypothalamus. No studies specifically demonstrate a role for norepinephrine in

effort-related decision making, but one report indicates that depletion of 5-HT does not affect performance in rats responding on the T-maze barrier choice task (Denk et al., 2005). Together with the present results, these studies support the hypothesis that the effects of tetrabenazine on effort-related choice are largely due to actions on DA.

In summary, tetrabenazine alters effort-related choice behavior, reducing food-reinforced lever pressing and biasing animals toward selection of the freely available chow at doses that did not affect food preference or consumption. The ability of tetrabenazine to affect effort-based decision making is consistent with research showing that other manipulations associated with depression, including stress (Shafiei et al., 2012) and administration of proinflammatory cytokines (Nunes et al., 2003b), can alter effort-based choice. The behavioral effects of tetrabenazine were attenuated by coadministration of an adenosine A_{2A} antagonist and the antidepressant bupropion. Future research should study the effort-related effects of additional antidepressant drugs with different pharmacological profiles. Consistent with studies demonstrating DAergic involvement in effort-related processes and with research implicating DA in motivational symptoms of depression (Rampello et al., 1991; Brown and Gershon, 1993; Treadway and Zald, 2011; Argyropoulos and Nutt, 2013; Soskin et al., 2013), tetrabenazine reduced extracellular DA and altered DARPP-32 signaling in both substance-P- and enkephalin-containing accumbens neurons. This research could have implications for understanding the neural circuits underlying effort-related motivational dysfunctions in depression, schizophrenia, and other disorders.

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(Figure legend continued.) **B, C**, Immunofluorescence double labeling of different forms of phosphorylated DARPP-32. **B**, pDARPP-32(Thr34) immunofluorescence is localized in enkephalin-positive neurons (yellow/orange areas of cells in merged photo), whereas pDARPP-32(Thr75) immunofluorescence activity is colocalized with substance P (yellow/orange areas of cells in merged photo). **C**, pDARPP-32(Thr34) is not present in substance-P-positive neurons (separate green and red cells in merged photo) and pDARPP-32(Thr75) is not colocalized with enkephalin immunofluorescence activity (separate green and red cells in merged photo).

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